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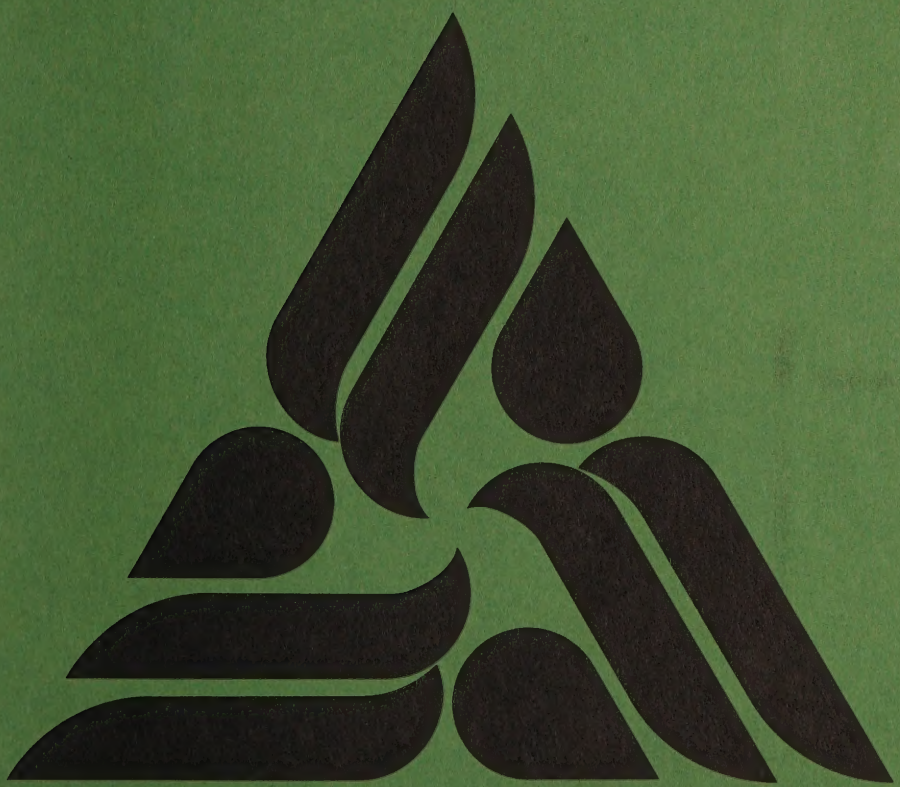
Minutes

Agricultural Biotechnology Research Advisory Committee

Classification and Confinement Working Group

December 2, 1991



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U.S. DEPARTMENT OF AGRICULTURE
Agricultural Biotechnology Research Advisory Committee

Working Group on Classification and Confinement
Minutes of Meeting
December 2, 1991

The Agricultural Biotechnology Research Advisory Committee (ABRAC) Working Group on Classification and Confinement (henceforth referred to as the Working Group) met on December 2, 1991, in the Cabinet Room of the Governor's House Holiday Inn, 17th and Rhode Island Avenue, N.W., in Washington, DC. Dr. John D. Kemp chaired the meeting. The meeting was open to the public and had been announced in the ***Federal Register***.

Members of the Working Group in attendance were Dr. John D. Kemp, chair; Dr. Harold Hafs; Dr. Anne Vidaver; Dr. William Witt; Dr. A. Ann Sorensen; and Dr. Deborah Letourneau. Dr. Bennie Osburn, ABRAC chair, also attended. Persons in attendance from the Office of Agricultural Biotechnology (OAB) were Alvin L. Young, Daniel Jones, Maryln K. Cordle, and Barry Stone.

Others in attendance were Dr. Bruce Umminger, National Science Foundation; Greg Dilworth, Department of Energy; Kent Reed, ***Food Chemical News***; Sarah Crim, Bureau of National Affairs; and Dr. David MacKenzie, National Biological Impact Assessment Program.

Call to Order and Preliminaries

Dr. Kemp called the meeting to order at 9:20 a.m. He asked that the agenda for the meeting be approved, and that any changes from the minutes of the Working Group's meeting of October 30 and 31 be submitted to OAB staff. The agenda was approved.

Status of the Guidelines

Dr. Kemp asked Ms. Cordle to update the Working Group on the status of the scope of the ***Proposed Guidelines for Research Involving Planned Introduction into the Environment of Genetically Modified Organisms*** (henceforth referred to as the Guidelines).

Ms. Cordle said that there had been no further activity on the scope issue from either leadership at the U.S. Department of Agriculture (USDA) or the President's Competitiveness Council since the Working Group's last meeting. She said that work on

the scope question would proceed as had been described at that meeting.

Ms. Cordle directed attention of the Working Group to a revised draft of the Guidelines prepared by the OAB (See Exhibit #159 included as Attachment A of these minutes). She noted that the Appendix, which consists of examples of how to use the Guidelines, was not included in that revision. She suggested that the examples be discussed later in the meeting.

Dr. Hafs asked if a successor to former Assistant Secretary of Agriculture for Science and Education Charles Hess had been chosen. Ms. Cordle answered that the Secretary of Agriculture reportedly was still interviewing candidates for the position, and that, in the meantime, Acting Assistant Secretary Harry Mussman had instructed OAB to proceed with completing the Guidelines.

Dr. Kemp predicted and Ms. Cordle agreed that no additional feedback on the Guidelines from USDA leadership was likely until a successor to Dr. Hess is named. Dr. Kemp then asked Ms. Cordle if she were uncomfortable with any areas of the revised draft of the Guidelines.

Ms. Cordle responded that the section dealing with the scope of the Guidelines would always cause controversy, particularly at the Office of Management and Budget (OMB). She also noted that the change in the title of the Guidelines from "Organisms with Deliberately Modified Hereditary Traits" to "Genetically Modified Organisms" had not been viewed favorably.

Dr. Osburn pointed out that the revised draft represented a significant rewrite of the Guidelines that had appeared in the ***Federal Register***, and asked if a second round of public comments would be necessary. Ms. Cordle said that answer would not be clear until the Guidelines were submitted to USDA's Office of General Counsel (OGC). She said that at her most recent meeting with OGC, she was told that the Guidelines should be submitted to the ***Federal Register*** as a Presentation Notice, and that a Companion Notice be used to propose implementation of the Guidelines. The preamble to the Guidelines will refer to both notices.

Dr. Vidaver and the rest of the Working Group complimented Ms. Cordle on her work in preparing the revised draft.

Dr. Kemp then began to lead the Working Group through a section-by-section review of the revised draft of the Guidelines.

Discussion: Title of the Guidelines

Dr. Kemp asked if the term "genetically modified organisms" in the title of the Guidelines was open to misinterpretation.

Dr. Hafs noted that another Working Group member, Dr. Sue Tolin, had asked if a simple manipulation of nucleic acids constituted a genetic modification. He understood the term "genetic modification" to mean "inheritable", and wondered if the use of the term "genetically modified organisms" in the title of the Guidelines makes this less clear. The Working Group agreed that the Guidelines' definition of "genetically modified organisms" would clear up any misunderstanding caused by the change in the title.

Dr. Letourneau asked if the term "field release" or "field test" should be used in the title. Ms. Cordle responded that the ABRAC had decided to use neither term, and instead had opted to use the term "planned introduction into the environment."

Ms. Cordle also asked that the examples not use the word "release", but instead use the words "planned," "controlled," or "managed" when discussing the introduction of genetically modified organisms into the environment. She explained that some people confuse the term "field release" with release of an organism into the open environment, i.e., a commercial release.

Discussion: Definitions and Acronyms

After discussion, the Working Group agreed to the following changes in Section II, Definitions and Acronyms:

Add to Section II a new term as follows:

> "Accesible environment" refers to the environment capable of being reached by the organism introduced at the research site(s).

Section II-A-2: Cross-reference Section II-A-8.

Section III-A-3: "Confinement." Remove "scope of."

Section II-A-4: In response to Dr. Vidaver's objection to the term "leaving," the phrase "to effectively restrict its movement outside the structure" replaces "is designed to restrict the organism from leaving."

Section II-A-8: A newer reference than Whittaker, 1969, is needed for the definition of microorganism. Insert "prions" before "and viruses." In the last sentence, insert "Prions, as

well as" before "viruses and subviral structures." Substitute "subviral structures" for "viral substructures."

Section II-A-9: Remove examples.

Section II-A-10: Replace "alterated" with "altered."

Section II-A-11: Find a later edition of ***Biology of Plants*** (1985) if possible. Clarify the multiple page number designation 961.718.

Section II-A-12: Add "at a designated site(s) with appropriate confinement" after "facilities." Rewrite second sentence to read, "It does not refer to the deliberate release of organisms beyond designated research sites or to commercial release."

Discussion: Scope

After discussion, the Working Group agreed to the following changes in Section III, Scope:

III-A, General: Delete the word "agricultural," and replace the phrase "II-A-1 through III-A-6" with III-A.

III-A-2: Insert the term "embryo fusion" after "embryo splitting." Dr. Osburn pointed out that embryo fusion had never posed any safety questions because there is no evidence that embryo fusion has ever resulted in a new type of animal.

III-A-3: Delete item (c), which already is covered in items (a) and (b). Suggested bringing to the full ABRAC a proposal to remove items (b)i and (b)ii, and rewrite Section III-A-3(b) to read as follows:

> (b) The movement of nucleic acids using the physiological processes including, but not limited to, transduction, transformation, or conjugation, provided that there has been no directed addition to or rearrangement of nucleic acids from the nucleotide sequences that have been moved.

The Working Group's recommendation to present to the full ABRAC these changes to Section III-A-3(b) came only after considerable debate.

The members of the Working Group who favored the changes believed that items (b)i and (b)ii are indeed physiological processes, although manipulated. These items described processes that scientists have performed for a decade or more, and no safety problem has occurred during that time.

Other members of the Working Group expressed concern that despite scientists' experience with these processes, something unexpected could result from them, and that removal of items (b)i and (b)ii crippled the capacity of the Guidelines to address this contingency. They felt it was important to ensure that the Guidelines do not unnecessarily cover those organisms for which there is no safety concern, but also do not fail to cover those organisms for which a legitimate safety concern exists.

Ms. Cordle pointed out that the language in items (b)i and (b)ii came from a report by the U.S. Environmental Protection Agency's (EPA) Biotechnology Science Advisory Committee (BSAC) subcommittee. The report deals with a proposed biotechnology rule for implementing the Toxic Substances Control Act (TSCA).

Dr. Hafs asked if removal of items (b)i and (b)ii from the USDA Guidelines would create problems with EPA. Ms. Cordle responded that TSCA requires EPA to emphasize the concept of newness. The USDA Guidelines do not flow from TSCA; therefore, the USDA Guidelines can and do emphasize the concept of familiarity with no statutory obligation to deal with the issue of newness.

III-A-4: Dr. Letourneau recommended that the microorganisms covered in this section include prions, in order to ensure consistency with Section II-A-8.

III-A-7: The Working Group asked why this section is included in the Guidelines. Ms. Cordle explained that this section is designed to provide for future exclusions from the Guidelines. Dr. Hafs said that future exclusions could be covered by USDA's Animal and Plant Health Inspection Service (APHIS).

Discussion: Section V

V, Overview: The Working Group recommended that the last sentence in the first paragraph (shown as deleted) not be removed but be revised to indicate three levels of safety concern. The Working Group agreed that if each attribute of the parental organism was to be rated numerically (e.g., (1) low conern, (2) moderate concern or (3) high concern), an explanation of the need to perform such a rating was needed in this section. However, the Working Group did not decide whether to require such ratings.

Discussion: Section VI

VI (overall): Dr. Vidaver suggested, and the Working Group agreed, that one or two sentences in the introductory part of this section should specify that each of the steps to determining the LSC for the parental organism involves making a quantitative assessment.

VI-A: Rewrite this section to read as follows:

> VI-A. ACTION I. Accessible Environment. Describe the environment capable of being reached by the organism in the absence of confinement beyond that inherent in the biology of the organism. Describe the characteristics of the area in and immediately surrounding the research site, and include the expected area of dispersal of the parental organism from that location.

This rewrite resulted from a draft presented by Drs. Letourneau and Vidaver at the request of Dr. Kemp, with additional changes suggested by members of the Working Group and Ms. Cordle. Dr. Kemp had asked for the draft after Drs. Letourneau and Vidaver said they believed that Section VI-A needed to be simplified.

VI-B: Substitute "describe" for "define". Remove the last sentence ("Furthermore ...").

VI-B-1-a: Dr. Letourneau suggested substituting "accessible environment" for "natural environment." Several members asked what "edaphic" means; Ms. Cordle said she would check the definition.

VI-B-2-a: Dr. Vidaver suggested that the word "adverse" be removed so that the Guidelines would deal with beneficial as well as adverse effects. The Working Group declined to adopt this suggestion.

VI-B-4-b: Delete "any." Dr. Vidaver asked if this section deals sufficiently with the consequences of genetic exchange. Dr. Hafs responded that Section VI-C does so.

VI-B-5-c: Dr. Vidaver suggested, and the Working Group agreed, to add "and to mitigate potential adverse effects" after "site." The Working Group also suggested that the National Environmental Policy Act (NEPA) be cited.

VI-D: Rewrite the first clause of the second sentence to read: "The three levels of safety concern are dependent on two criteria ..." In the second paragraph, fourth sentence make "organisms" singular; delete comma preceding "would only be a concern...."

VI-D-2: Dr. Vidaver suggested deleting "unacceptable" and substituting "some" or "significant." The Working Group agreed to delete "unacceptable," and to consider a substitute word at a later time.

The Working Group also agreed to remove "but", and insert "and must" between "can" and "be."

VI-D-3-b and VI-D-3-d: Add "with adverse effects" to the end of each section.

Discussion: Section VIII

VIII: Rewrite the first sentence to read as follows:

> In Step 3, principal investigators should assign to the genetically modified organism one of three levels of safety concern ...
>
> Substitute "if" for "whether."

VIII-A-1 and VIII-A-2: Substitute "conduct" for "achieve."

VIII-C: Replace "LSC-2" with "LSC-3." Insert Table 1 at the end of Section VII-C and its subparts.

VIII-C-1-c: Replace "increases safety" with "decreases safety concern."

Discussion: Section IX

IX: In the second paragraph, delete "scope of."

IX-A: In the second paragraph, replace "utilized apply" with "used." In the third paragraph, insert "feed for" between "or" and "animals."

IX-B-1: Rewrite the last sentence to read as follows:

> Permitting natural biological decay, e.g. normal death, can be an effective approach.

IX-B-3: Rewrite this section to read as follows:

> IX-B-3. Physical. Physical barriers or measures can be used to limit the survival and dissemination of organisms outside the research site. These include border rows, dams, soil terraces, tillage, fences, screens, meshes, and impervious or plastic barriers.

IX-C-2: Replace "prevented" with "controlled."

Wrap-Up and Adjournment

Because the section-by-section review of the Guidelines had taken the entire day allotted to the Working Group meeting, Dr. Kemp suggested that the review of the examples be dealt with in the

full ABRAC. He asked the members of the Working Group to rewrite their examples in light of the changes to the Guidelines made during the day's review.

Ms. Cordle asked the members to use Roman numerals when re-drafting their examples, to remove any references to "good agricultural practices," and to explain more thoroughly their reasons for assigning various LSC's.

Dr. Kemp adjourned the meeting at 5:20 p.m.

Approved:

SUSAN McCULLOUGH
Rapporteur

DANIEL JONES
Editor

ALVIN YOUNG
Executive Secretary

JOHN KEMP
Chair

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ATTACHMENT A

November 18, 1991

TO: Members of the Agricultural Biotechnology Research Advisory Committee

SUBJECT: Revised Draft of the Guidelines

Attached please find a revised draft of the "USDA Guidelines for Research Involving Planned Introduction Into the Environment of Genetically Modified Organisms.

The redlined (shadow) text indicates additions to the proposal published in the *Federal Register* of February 1, 1991 (56 FR 4134), and the strikeout shows deleted text. The ABRAC Working Group on Classification and Confinement is still working on Appendix 1, which will include examples of specific organisms carried through the four step assessment procedure. As soon as Appendix 1 is completed, it will be sent to you.

The Working Group will discuss the draft guidelines at its meeting on December 2, and report its recommendations during the meeting of the full ABRAC on December 3. Although the full ABRAC Committee will have an opportunity to discuss the draft, if there are particular points you want to have the Working Group address, you should convey that request to the Dr. John Kemp, Chairman of the Working Group.

You will note that specific definitions of scope have been added based on discussions at the October meeting of the ABRAC Working Group. The Working Group was provided with background materials on Scope to assist them in the discussion. If any of you would like this information, please call the OAB office (703) 235-4419.

If I can be of further assistance to you in preparing for discussion of the Guidelines, please call me at (703) 235-1510.

Sincerely,

Maryln Cordle

Maryln K. Cordle
Sr. Regulatory Specialist

[*Comparison Draft, November 18, 1991*]

~~Proposed~~ USDA Guidelines For Research Involving Planned Introduction Into The Environment Of Genetically Modified Organisms ~~With Deliberately Modified Hereditary Traits~~

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VI-B-3. Other Ecological Relationships with Other Organisms in the Accessible Environment

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VIII. Step 3: Determination of the Level of Safety Concern for Genetically Modified Organisms ~~with Deliberately Modified Hereditary Traits~~

I. Purpose

These Guidelines recommend practices and procedures for the safe conduct of research involving the planned introduction into the environment of certain genetically modified organisms ~~with deliberately modified hereditary traits~~. The Guidelines establish principles for assessing the safety of research with specific organisms and designing confinement to promote safety. They are intended to aid

researchers and institutions in the design of safe experiments conducted outside of contained facilities.

II. Definitions and Acronyms

II-A. Technical Terms

II-A-1. "Animal" is any member of the Kingdom Animalia, which includes vertebrates and invertebrates as defined in Raven, Peter M. and George B. Johnson (1986). "Biology". Times Mirror/Mosby Publishing. St Louis, MO. p. 724.

II-A-2. "Cellular microorganisms" refers to microorganisms other than viruses and subviral structures such as viroids.

~~II-A-3~~. ~~II-A-1~~. "Confinement" is that which restrains or limits the scope of spread or survival of organisms and their products in research involving planned introduction of organisms into the environment. (See Section IX.)

II-A-4. ~~II-A-2~~. "Contained facility" refers to a structure ~~an enclosed structure with walls, roof, and floor~~ (e.g., a laboratory or greenhouse) which effectively surrounds and encloses the organism and is designed to restrict the organism from leaving, as ~~that is~~ described in the National Institutes of Health "Guidelines for Research Involving Recombinant DNA Molecules," (Federal Register, May 7, 1986, 51 FR 16958).

II-A-5. "Genetically modified organism" is operationally defined as an organism whose hereditary traits

have been modified by human intervention using any method that results in the introduction, rearrangement, or removal of genetic material from the genome of an organism.

II-A-6. "Genome" means the sum total of chromosomal and extra-chromosomal genetic material of a specific organism. In the case of a microorganism it means the sum total of chromosomal and extra-chromosomal genetic material of an isolate and any descendants derived under pure culture conditions from that isolate.

II-A-7. ~~II-A-3~~. "Managed or natural ecosystems" refers to all plants, animals, and microorganisms, and their interactions, in domesticated and wild environments.

II-A-8. "Microorganism" means any organism classified in the kingdoms Monera, Protista, and Fungi, the Chlorophyta and the Phodophyta of the Plantae (as defined by R. H. Whittacker, 1969, "New concepts of kingdoms of organisms", Science, 163:150-160), and viruses and viral substructures. These organisms include, but are not limited to, bacteria, protozoa, fungi, mycoplasmas, mycoplasma-like organisms, spiroplasmas, microphytoplanktons, green and red algae. Viruses and subviral structures such as viroids are also considered microorganisms even though they are not ordinarily classified in the taxonomic system applied to other organisms.

II-A-9. ~~II-A-4~~. "Organism" is any biological entity, cellular or noncellular, with the capacity for self-

perpetuation and response to evolutionary forces; examples include plants, animals, fungi, prokaryotes, viruses, and viroids. ~~(To avoid repetition in the use of "organisms and its products," the term "organism" includes not only the living organism but any substance such as toxins produced by the organism.)~~

II-A-10. "Parental organism" refers to the initial organism which is to be the recipient of introduced genetic material or whose genome is to be alterated by removal or rearrangement of genetic material.

II-A-11. "Plant is any member of the Kingdom Plantae, made up of bryophytes and vascular plants, as defined in Raven, Peter H., Ray F. Evert, and Susan E. Ichborn (1985). "Biology of Plants". Worth Pub. Inc. New York, NY. pp. 961.718.

II-A-12. ~~II-A-7~~. "Research involving planned introduction into the environment" refers to research outside contained facilities in an appropriately confined environment. (See Section IX.) It does not refer to the deliberate release of organisms in the open environment beyond research sites or to releases in a commercial setting.

II-A-13. ~~II-A-5~~. "Safety" or "safe" refers to conditions determined with reasonable certainty to have acceptable or negligible risk to human health or to managed or natural ecosystems.

~~II-A-6. "Deliberately modified hereditary traits" refers to changes to genetic traits of an organism by any method.~~

II-B. Administrative Terms

II-B-1. "ABRAC" or "Agricultural Biotechnology Research Advisory Committee" is a Federal advisory committee that advises the Secretary of Agriculture through the Assistant Secretary for Science and Education on scientific and technical matters concerning biotechnological research, including research involving the planned introduction into the environment of genetically modified organisms ~~with deliberately modified hereditary traits~~.

II-B-2. "Department" refers to the United States Department of Agriculture.

II-B-3. "IBC" or "Institutional Biosafety Committee" is a ~~the~~ committee at an institution that provides local expertise in aiding researchers in the use of the Guidelines. (See Section X-B.)

II-B-4. "Institution" refers to any individual, corporation, partnership, association, public or private entity, Federal agency, or other unit which conducts or sponsors research. (See Section X-A.)

II-B-5. "OAB" or "Office of Agricultural Biotechnology" is the office within the United States

Department of Agriculture which serves as the point of contact for users of the Guidelines.

II-B-6. "USDA" refers to the United States Department of Agriculture.

III. Scope

III-A. General

~~These guidelines are intended for agricultural research involving the planned introduction into the environment of certain organisms with deliberately modified hereditary traits. The Office of Science and Technology Policy, Executive Office of the President, on July 31, 1990, published for comment proposed "Principles for Federal Oversight: Planned Introduction into the Environment of Organisms with Modified Hereditary Traits." Upon consideration of comments on both this document and the OSTP document, appropriate examples will be published describing the types of environmental research with organisms with deliberately modified hereditary traits for which use of these guidelines is not necessary or appropriate.~~

These guidelines are intended for agricultural research involving the planned introduction into the environment of organisms that have been deliberately modified by alteration of their genome, except as defined in III-A-1 through III-A-6.

III-A-1. Plants that result solely from: (a) selection, natural regeneration or traditional breeding

techniques, including hand pollination or other managed, controlled pollination; (b) chemical or physical mutagenesis, and (c) plants that are regenerated from organ, tissue, or cell culture, including those produced through selection and propagation of somaclonal variants, embryo rescue, protoplast fusion, or ploidy manipulation.

III-A-2. Animals that result solely from selection, artificial insemination, superovulation, embryo transfer, embryo splitting, or ploidy manipulation.

III-A-3. Cellular microorganisms modified in hereditary traits solely by one of the following means:

(a) Chemical or physical mutagenesis.

(b) The movement of nucleic acids using the physiological processes including, but not limited to, transduction, transformation, or conjugation. To qualify as a physiological process, all of the following criteria must be met: (i) the recipient microorganism has not lost the ability to recognize and cleave foreign DNA; (ii) the recipient microorganism has not been exposed to conditions to induce competence artificially by treatments that render the microorganism permeable to transforming DNA; and (iii) there has been no directed addition to or rearrangement of nucleic acids from the nucleotide sequences that are moved.

(c) By plasmid loss or spontaneous deletion.

III-A-4. Microorganisms resulting from deletions, rearrangements, and amplifications, within a single genome, including its extra-chromosomal elements. Rearrangements are translocations and inversions of nucleotide sequences in the genome. This exclusion does not apply if the microorganism is deliberately modified to have (i) increased virulence or toxin production, (ii) significant changes in competitive ability or environmental requirements, or (iii) phenotypic properties that are harmful to humans or would adversely alter the environment.

III-A-5. Organisms modified by the introduction of non-coding, non-expressed nucleotide sequences that cause no phenotypic or physiological changes in the recipient microorganisms. Non-coding, non-expressed nucleotide sequences that cause no phenotypic or physiological changes in the recipient organism means the nucleotide sequences are not transcribed and are not involved in gene expression or replication and include linkers, homopolymers, adaptors, and flanking sequences.

III-A-6. Microorganisms that have resulted from combinations of sections III-A-4 and III-A-5.

III-A-7. [Reserved]

III-B. Research Subject to Regulations

~~Certain field testing involving specific organisms such as pathogens or pesticides may be subject to the~~

~~jurisdiction of a Federal regulatory agency and requires its prior approval or clearance.~~ Research involving introduction into the environment of many of the organisms included within the scope of these guidelines is subject to the jurisdiction of a Federal regulatory agency and requires prior approval or clearance. This includes, for example, regulation by USDA's Animal and Plant Health Inspection Service of plant pests and potential plant pests, and other organisms under the Virus, Serum Toxin Act, and regulation by the U.S. Environmental Protection Agency of microbial pesticides and other microorganisms under the Toxic Substances Control Act. Questions concerning jurisdiction of Federal agencies may be addressed to OAB. Although the guidelines may be useful to investigators preparing submissions to regulatory agencies, adherence to the Guidelines should not be viewed as a substitute for full compliance with all regulatory requirements.

IV. General Information

The Guidelines are based upon current ~~agricultural~~ knowledge and practices for safe planned introduction of genetically modified organisms into the environment ~~field research~~. USDA will periodically revise the Guidelines in accordance with the amendment procedures in section XI to reflect new scientific information.

V. Overview: Guidelines for Safe Conduct of Research

The purpose of this section is to provide an overview of the scheme, or step-wise process, that is recommended for use by ~~the~~ principal ~~principle~~ investigator~~s~~. The conditions under which research with a genetically modified ~~an~~ organism ~~with deliberately modified hereditary traits~~ can be conducted safely should be assessed relative to the conditions that are normally accepted for conducting research with the parental organism. Therefore, the safety evaluation begins in Section VI with a determination of the level of safety concern for the parental organism in a specific, described environment. ~~Section VI sets out a framework for determining which of five levels of safety concern is appropriate for the parental organism in a specific environment.~~

After the level of safety concern for the parental organism has been determined, the principal investigator should consider the effect of the genetic modification on safety. Section VII sets out a framework for assessing whether the modification has no effect on ~~the level of~~ safety ~~concern~~, or whether it increases or decreases safety ~~the level~~. Knowledge of the precise modification may allow better predictability of the safety of the organism and its products, so that appropriate confinement and other safety practices for the research can be selected.

Evaluation of the effect of the genetic modification on the biological and ecological attributes of the parental organism will lead to the determination of the level of safety concern for the modified organism. This guidance is provided in Section VIII.

At this point, principal investigators should choose appropriate confinement measures, based on the biological and ecological attributes of the modified organism. ~~assign an appropriate confinement level, based on the level of safety concern for the modified organisms and design the confinement measures and other safety conditions for the research.~~ Section IX describes confinement principles that can be applied to the design of safety protocols ~~the research~~ to achieve research with acceptable or negligible risk. ~~appropriate levels of confinement.~~

In summary, the conditions for safely performing research should be chosen according to the following four step process:

Step 1. Determination of the level of safety concern for the parental organism (Section VI).

Step 2. Determination of the effect of the genetic modification on the level of safety concern, i.e., whether it increases, decreases, or has no effect on the level of safety concern for the parental organism (Section VII).

Step 3. Determination of the level of safety concern for the modified organism (Section VIII).

Step 4. Determination of the confinement measures ~~level~~ appropriate to the particular biological and ecological attributes of ~~level of safety concern for~~ the genetically modified organism and development of a safety protocol ~~to meet the level of confinement~~ (Section IX) so that planned introduction into the environment is managed to achieve acceptable or negligible risk.

Examples of organisms evaluated by this process are provided in Appendix 1.

VI. Step 1: Determination of the Level of Safety Concern for Parental Organisms

The level of safety concern for the parental organism should be determined by evaluating the attributes of the organism within the context of the environment in which the research is to be performed. (See Section VI-A.) The particular attributes of the organism should be studied along with its ecological relationships with other organisms in that ~~the~~ environment ~~accessible to it in the absence of confinement~~. The attributes which should be considered are:

- the potential of the parental organism to establish itself in the accessible environment,
- the pest/pathogen status and potential of the parental organism in the accessible environment,

~~- the potential of the parental organism to establish itself in the accessible environment,~~

- other ~~the~~ ecological relationships of the parental organism with other organisms in the accessible environment,
- the potential of the parental organism for inducing genetic change in natural or managed populations in the accessible environment, and
- the potential for monitoring and control of the parental organism in the accessible environment.

A series of actions is ~~are~~ recommended in the section to determine the level of safety concern for ~~of~~ the parental organism. By following these actions, principal investigators will be in a reasonable position to evaluate the relative importance of specific attributes, to choose a level of safety concern for the parental organism, and to document the rationale for placing the parental organism at a particular ~~an appropriate~~ level of safety concern. ~~Appendix 1 provides examples of specific organisms for further guidance to principal investigators in determining levels of safety concern.~~

The evaluations made under this section will not be the same for all organisms. Nor will all evaluations described in this section be relevant to every organism. At the same time, there may be additional information relevant to the

level of safety concern for a particular organism that is not specifically mentioned in this section.

VI-A. ACTION I. Accessible Environment. Define the environment accessible to the organism. This includes the area in and immediately surrounding the research site, into which the parental organism would have access in the absence of confinement measures beyond those inherent in the biology of the organism and the environmental characteristics of the particular site.

VI-B. ACTION II. Attributes of the Organism. Define the relevant attributes of the parental organism in the accessible environment. This should be done by addressing the questions and issues presented in this section. As noted above, the evaluation will differ among different organisms. Not all questions are relevant to all organisms. Furthermore, affirmative answers do not necessarily indicate a particular outcome in terms of determining the safety of the research.

VI-B-1. Potential to Establish Itself in the Accessible Environment

VI-B-1-a. What are the known mechanisms of survival or persistence of the organism in the natural environment? Are there natural predators or other organismal relationships that affect its survival? Are there climatic and edaphic or other abiotic factors influencing survival of the organism?

VI-B-1-b. What are the known mechanisms of dissemination of the parental organism?

VI-B-1-c. Is population size known to affect the ability of the organism to become established?

VI-B-1-d. What information is known about the competitiveness and aggressiveness of the organism in the accessible environment in relation to the ability of the organism to become established in that environment?

VI-B-2. ~~VI-B-1~~. Pest/Pathogen Status and Potential in the Accessible Environment

VI-B-2-a. ~~VI-B-1-a~~. What are the plausible adverse effects of the organism on the accessible environment due to its being a pest or pathogen? These include adverse effects, such as, lowered productivity of economically important organisms, damage or destruction of natural habitats, and adverse effects on human health. Will the potential extent of adverse effects, as a result of this research, be greater than already exists in the accessible environment from the organisms already present?

VI-B-2-b. ~~VI-B-1-b.~~ What is the potential for exchange of genetic information between the organism and pests or pathogens in the accessible environment? In other words, what is the likelihood of the organism becoming a pest or pathogen through an exchange of genetic information under the conditions of the research?

VI-B-2-c. ~~VI-B-1-c.~~ Does the organism have any ecological characteristics that might increase or decrease its pest/pathogen potential? For example, if the organism and its relatives were restricted to a narrow set of ecological conditions (niche), does this imply that the potential to broaden that niche and become a pest is expected to be low?

~~VI-B-2. Potential to Establish Itself in the Accessible Environment~~

~~VI-B-2-a. What are the known mechanisms of survival or persistence of the organism in the natural environment? Are there natural predators or other organismal relationships that affect its survival? Are there climatic and edaphic or other abiotic factors influencing survival of the organism?~~

~~VI-B-2-b. What are the known mechanisms of dissemination of the parental organism?~~

~~VI-B-2-c. Is population size known to affect the ability of the organism to become established?~~

~~VI-B-2-d. What information is known about the competitiveness and aggressiveness of the organism in the accessible environment in relation to the ability of the organism to become established in that environment?~~

VI-B-3. Other Ecological Relationships with Other Organisms in the Accessible Environment

VI-B-3-a. What is the importance of the organism to the structure of the community? Is the parental organism

involved in any critical ecosystem functions, e.g., nitrogen fixation, inorganic nutrient uptake, key food chain component, critical habitat for key species? Is involvement in critical ecosystem functions indirect or direct? Can other organisms in the ecosystem fulfill its function?

VI-B-3-b. What is the ecological specificity and range of interactions of the organism with other organisms?

VI-B-3-c. What is the geographic range of the organism? Is the geographic range small or large? What changes might occur in the organism to broaden or narrow its geographic range?

VI-B-3-d. What is the habit of the organism? Is the organism free-living, mutualistic, pathogenic, parasitic, or symbiotic? Does its habit relate to potential adverse effects on the environment should it escape from confinement? Will the habit of the organism facilitate monitoring and control?

VI-B-4. Potential for Inducing Genetic Change in Natural or Managed Populations in the Accessible Environment

VI-B-4-a. Is there intrinsic genetic stability of the genome? Can the organism incorporate exogenous DNA? Are active transposable elements present? Are active viral elements present that interact with the normal genome? Have mutations been observed that have resulted in an unusual genotype or phenotype?

VI-B-4-b. Is there a natural or managed interbreeding population known? What is its size? What is the degree of genetic diversity in the population? Is there any potential for genetic exchange between a "released" organism and the organisms in the natural population?

VI-B-5. Potential for Monitoring and Control in the Accessible Environment

VI-B-5-a. Is information from prior research (both within and outside contained facilities) available that has demonstrated control of the organism by various means, such as, biological, environmental, physical, chemical?

VI-B-5-b. What monitoring methods are available? What is their sensitivity and degree of accuracy? What is their cost?

VI-B-5-c. Are there procedures to minimize escape of the organism from the test site?

VI-C. ACTION III. Relative Importance of Attributes

Determine the relative importance of the specific attributes in the context of the planned research. Analyze the attributes to identify those that are most critical or influential in the determination of safe research conditions. ~~ability of the organism to cause adverse effects.~~

VI-D. ACTION IV. Level of Safety Concern

Determine the level of safety concern for the parental organism. The level of safety concern is dependent on two

criteria: (1) whether the organism poses acceptable or negligible risk to human health or to managed or natural ecosystems, and (2) the ability to manage and control the organism during its planned introduction into the environment so that the research is conducted safely. ~~The level of safety concern is based on the potential for adverse effects on human health or on managed or natural ecosystems. The level of safety concern is not derived from the sum or the mean of the individual levels assigned to the specific attributes described in Action II (Section VI B). Neither is it controlled by the highest or lowest levels assigned to the individual attributes.~~

The particular attributes listed, which indicate levels of safety concern, are not exclusive. ~~in Sections VI D 1 and VI D 5 which describe Levels of Safety Concern 1 and 5, respectively, are not exclusive.~~ Other attributes may also indicate a particular level. Furthermore, the presence of any one attribute does not necessarily indicate a particular level, ~~any one attribute does not necessarily indicate a particular level,~~ and all attributes listed need not be shown to conclude a particular level. For example, an organisms that may readily become established in the accessible environment, would only be of concern if other attributes indicate that such establishment would result in an unacceptable risk. Principal investigators must exercise sound scientific judgement in evaluating the relative

importance of the attributes in Action III (Section VI-C) in order to assign the level of safety concern.

~~When there is a question about the determination of the appropriate level of safety concern (e.g., choosing between Level 3 and Level 4), principal investigators should assign the higher level (i.e., choose Level 4).~~

VI-D-1. Level of Safety Concern 1 (LSC-1) Organisms. Organisms whose ecological attributes in the specified accessible environment are understood to the extent that it can be determined with reasonable certainty that the parental organism poses acceptable or negligible risk to ~~has virtually no potential for adverse effects on~~ human health or to ~~on~~ managed or natural ecosystems. No confinement measures are required beyond those inherent in the biology of the organism and the environmental characteristics of the particular site. Some attributes that alone or in combination might indicate LSC-1 ~~Level 1~~ organisms are:

VI-D-1-a. No history of adverse effects in the accessible environment or similar environments,

VI-D-1-b. Low evolutionary potential to become a harmful organism in the accessible environment,

VI-D-1-c. Low probability of survival in the accessible environment beyond the time necessary for the particular research,

~~VI-D-1-d. Low probability of exchange of genetic information with native populations of organisms,~~

~~VI-D-1-e. Indigenous status in the accessible environment,~~

~~VI-D-1-f. Existence of practical techniques to minimize escape of viable organisms from the accessible environment, or~~

~~VI-D-1-g. Existence of practical techniques to recapture or kill escaped organisms before adverse effects occur.~~

VI-D-2. Level of Safety Concern 2 (LSC-2) Organisms. Organisms whose ecological attributes in the specified accessible environment may pose unacceptable risk to human health or to managed or natural ecosystems, but which can be managed or controlled by appropriate confinement or other measures to achieve a level of safety concern equivalent to LSC-1. ~~Organisms which may cause adverse effects on human health or on managed or natural ecosystems, the consequences of which are predictably low.~~

VI-D-3. Level of Safety Concern 3 (LSC-3) Organisms. Organisms whose ecological attributes in the specified accessible environment may pose unacceptable risks to human health or to managed or natural ecosystems, and no feasible types of confinement will ensure safe conduct of the research outside contained facilities with reasonable certainty at this time. ~~Organisms which may cause adverse effects on human health or on managed or natural ecosystems, the consequences of which are predictably moderate.~~

~~VI-D-4. Level 4. Organisms which may cause adverse effects on human health or on managed or natural ecosystems, the consequences of which are predictably high.~~

~~VI-D-5. Level 5. Organisms whose ecological attributes in the specified accessible environment indicate the organism may cause adverse effects on human health or on managed or natural ecosystems, the consequences of which are predictably high, and no feasible types of confinement will allow safe conduct of research outside contained facilities.~~ Some of the attributes that alone or in combination might indicate LSC-3 ~~Level 5~~ organisms are:

VI-D-3-a. ~~VI-D-5-a.~~ History of adverse effects in the specified accessible environment or in similar environments,

VI-D-3-b. ~~VI-D-5-b~~. Ability to survive and proliferate in the specified accessible environment,

VI-d-3-c. ~~VI-D-5-c~~. Non-indigenous status in the accessible environment,

VI-D-3-d. ~~VI-D-5-d.~~ High frequency of exchange of genetic information with native populations of organisms,

VI-D-3-e. ~~VI-D-5-e.~~ Lack of effective techniques to minimize escape of viable organisms or active products of the organism from the research site, or

VI-D-3-f. ~~VI-D-5-f.~~ Lack of adequate techniques to recapture or kill escaped organisms before adverse effects occur.

VII. Step 2: Determination of the Effect of the Genetic Modification on Level of Safety Concern

The genetic modification should be evaluated in terms of its effects on the attributes of the parental organism ~~evaluated in Step 1~~. Genetic modification may have no effect on ~~the level of~~ safety ~~concern for the organism~~, or it may increase or decrease ~~the level of~~ safety ~~concern~~. The genetic modification might alter the safety of the organism without changing the level of safety concern. For example, a specific modification of a LSC-2 parental organisms may reduce the safety concern, but certain confinement measures may still be necessary to achieve research with acceptable risk and, therefore the modified organism may remain at the same level of safety concern (i.e., LSC-2). The effects of the genetic modification on safety must be evaluated with reference ~~both~~ (i) to the direct effects ~~actions~~ of the organism on human health or the environment, (ii) ~~and~~ to the indirect effects ~~actions~~ of the organism through the substances it produces, and (iii) to effects resulting from exchange of genetic material with other organisms in the accessible environment.

In Step 2, principal investigators should examine the method of genetic modification; the molecular characterization and stability of the modified genes; and the expression, functions, and effects of the modified genes. Although the process of modifcation alone is not a

determinant of safety, such ~~This~~ information can facilitate ~~allows a~~ determination of whether the genetic modification decreases the ~~level of~~ safety concern for the modified organism (Type 1), has no effect on the ~~level of~~ safety concern (Type 2), or increases the ~~level of~~ safety concern (Type 3).

VII-A. Type 1: Genetic Modifications that Decrease the ~~Level of~~ Safety Concern for the Modified Organism

Type 1 modifications include those which delete or disrupt expression of a gene or genes known to be responsible for traits, such as, pathogenicity, fertility, survival, or fitness, in ways that increase safety of the organism. Substantial understanding of the molecular biology or other information, including relevant experience, which show that the modification is well characterized and that the gene functions and effects are adequately understood to predict safety, should be demonstrated before a Type 1 determination is made.

VII-B. Type 2: Genetic Modifications that Have No Effect ~~on the Level of~~ Safety Concern for the Modified Organism

Substantial understanding of the molecular biology or other information, including relevant experience, which show that the modification is well characterized and that the gene functions and effects are adequately understood to

predict safety, should be demonstrated before a Type 2 determination is made.

Type 2 modifications include:

VII-B-1. Insertions of nucleic acid from any source, deletions, or rearrangements that have no phenotypic or genotypic consequence in the accessible ~~environment field~~, e. g., certain marker genes bearing no hazardous traits, and

VII-B-2. Insertions of nucleic acid from any source, deletions, or rearrangements that have known or predictable phenotypic or genotypic consequence in the accessible ~~environment field~~ that is unlikely to result in additional adverse effect on human health or on managed or natural ecosystems, e.g., a storage protein gene with a more desirable amino acid balance.

VII-C. Type 3: Genetic Modifications that Increase the ~~Level of~~ Safety Concern for the Modified Organism

Type 3 modifications include:

VII-C-1. Insertions of nucleic acid from any source, deletions, or rearrangements that affect the expression of genes, but the functions or effects are not sufficiently understood to determine with reasonable certainty whether the modified organism poses greater risk than the parental organism ~~of which are not well understood~~, and

VII-C-2. Insertions of nucleic acid from any source, deletions, or rearrangements that have known or predictable phenotypic or genotypic consequence in the accessible

environment ~~field~~ that is likely to result in additional adverse effects on human health or on managed or natural ecosystems, e.g., those which result in the production of certain toxins.

VIII. Step 3: Determination of the Level of Safety Concern for Genetically Modified Organisms ~~With Deliberately Modified Hereditary Traits~~

In Step 3, principal investigators should determine the level of safety concern for the genetically modified organism by considering the effect of the genetic modification (Section VII) on safety and whether the attributes affected, if any, alter the level of safety concern for the modified organism compared to ~~for~~ the parental organism (Section VI). The level of safety concern for the genetically modified organism is dependent on the same criteria applied to the determination of the level of safety concern for the parental organism, namely: (1) whether the organism poses acceptable or negligible risk to human health or to managed or natural ecosystems, and (2) the ability to manage and control the organism during its planned introduction into the environment so that the research is conducted in a safe manner. ~~The level of safety concern for genetically modified organisms is based on the effects of the modification on the potential for adverse effects on human health or on managed or natural ecosystems. Information evaluated in Step 2 on molecular biology and~~

~~gene expression, which allows greater predictability of the safety of the modified organism, should be used in each case to determine the level of safety concern for the modified organism.~~

~~When there is a question about assignment of the appropriate level of safety concern (e.g., choosing between Level 4 and Level 3) principal investigators should assign the higher level (i.e., Level 4). The following describes the possible levels of safety concern for modified organisms. A description of this is presented in Table 1.~~

VIII-A. LCS-1 ~~Level 1~~ Parental Organisms~~.~~

VIII-A-1. LSC-1 parental organisms with ~~With~~ Type 1 modifications remain LSC-1 genetically modified organisms. No confinement measures are required beyond those inherent in the biology of the organism and the environmental characteristics of the particular site to achieve research with an acceptable risk. ~~result in Level 1 modified organisms.~~

VIII-A-2. LSC-1 parental organisms with ~~With~~ Type 2 modifications ~~result in Level 1 will~~ remain LSC-1 genetically modified organisms. No confinement measures are required beyond those inherent in the biology of the organism and the environmental characteristics of the particular site to achieve research with an acceptable risk.

VIII-A-3. LSC-1 parental organisms with ~~With~~ Type 3 modifications result in LSC-1, LSC-2, or LSC-3 ~~Level 2, 3, 4, or 5~~ genetically modified organisms, depending on the degree of increased safety concern.

VIII-A-3-a. If the risk of introduction of the organism into the environment remains acceptable without the need for additional confinement measures, even though the Type 3 modification increases the safety concern, the genetically modified organism remains LSC-1.

VIII-A-3-a. If the Type 3 modification increases the safety concern to the extent that risk of introduction of the organism into the environment is no longer acceptable, but feasible confinement and other measures are available so that the research can be conducted with acceptable risk, the genetically modified organism is LSC-2.

VIII-A-3-c. If the Type 3 modification increases safety concern to the extent that introduction into the environment cannot be adequately managed or controlled to achieve acceptable risk, the genetically modified organism is LSC-3. Research with the organism must remain in containment until there is a reasonable certainty that planned introduction into the environment can be managed and controlled to achieve acceptable risk.

VIII-B. LSC-2 ~~Level 2~~ Parental Organisms~~+~~

VIII-B-1. LSC-2 parental organisms with ~~With~~ Type 1 modifications result in LSC-1 ~~Level 1~~ or LSC-2 genetically

modified organisms, depending on the degree of decrease in safety concern.

VIII-B-1-a. If the Type 1 modification decreases the safety concern to the extent that the organism poses acceptable risk without the need for confinement measures beyond those inherent in the biology of the organism and the environmental characteristics of the particular site, the genetically modified organism is LSC-1.

VIII-B-1-b. If the risk of introducing the organism into the environment remains acceptable only when managed by use of additional confinement measures, even though the Type 1 modification decreases the safety concern, the genetically modified organism is LSC-2.

VIII-B-2. LSC-2 parental organisms with ~~With~~ Type 2 modifications remain ~~result in Level 2~~ LSC-2 genetically modified organisms. Appropriate confinement measures are necessary for planned introduction into the environment with acceptable risk.

VIII-B-3. LSC-2 parental organisms with ~~With~~ Type 3 modifications result in LSC-2 or LSC-3 ~~Level 3, 4, or 5~~ genetically modified organisms, depending on the degree of increase in safety concern.

VIII-B-3-a. If the Type 3 modification increases the safety concern, but the planned introduction into the environment still can be managed or controlled by

appropriate confinement measures to achieve acceptable risk, the genetically modified organim remains LSC-2.

VIII-B-3-b. If the Type 3 modification increases safety concern so that there is not a reasonable certainty that planned introduction into the environment can be managed or controlled to achieve acceptable risk, the genetically modified organism is LSC-3. Research with the organism must remain in containment until its planned introduction into the environment can be managed and controlled to achieve acceptable risk.

VIII-C. LSC-1 ~~Level 3~~ Parental Organisms~~:~~

VIII-C-1. LSC-3 parental organisms with ~~With~~ Type 1 modifications result in LSC-1, LSC-2, or LSC-3 ~~Level 1 or 2~~ genetically modified organisms, depending on the degree of decrease in safety concern.

VIII-C-1-a. If the Type 1 modification decreases safety concern to the extent that planned introduction into the environment poses acceptable risk without confinement measures beyond the inherent biology of the organism or the environmental characteristics of the research site, the genetically modified organism is LSC-1.

VIII-C-1-b. If the Type 1 modification decreases safety concern but additional confinement measures are necessary for planned introduction into the environment with acceptable risk, the genetically modified organism is LSC-2.

VIII-C-1-c. If the Type 1 modification increases safety but not to the extent that planned introduction of the organism can be managed and controlled to achieve acceptable risk, the genetically modified organism remains LSC-3. Research must be conducted in a contained facility until planned introduction into the environment can be adequately managed and controlled to achieve acceptable risk.

VIII-C-2. LSC-3 parental organisms with ~~With~~ Type 2 or Type 3 modifications remain LSC-3 ~~result in Level 3~~ genetically modified organisms.

~~VIII-C-3. With Type 3 modifications result in Level 4 or 5 modified organisms.~~

~~VIII-D. Level 4 Parental Organisms:~~

~~VIII-D-1. With Type 1 modifications result in Level 1, 2, or 3 modified organisms.~~

~~VIII-D-2. With Type 2 modifications result in Level 4 modified organisms.~~

~~VIII-D-3. With Type 3 modifications result in Level 5 modified organisms.~~

~~VIII-E. Level 5 Parental Organisms:~~

~~VIII-E-1. With Type 1 modifications result in Level 1, 2, 3, or 4 modified organisms.~~

~~VIII-E-2. With Type 2 modifications result in Level 5 modified organisms.~~

~~VIII-E-3. With Type 3 modifications result in Level 5 modified organisms.~~

IX. Step 4: Confinement Principles and Design of Safety Protocols

Principal investigators should select appropriate measures ~~and level~~ of confinement for the genetically modified organism, as indicated by the biological and ecological attributes of the organism and the level of safety concern.

Confinement measures that restrain or limit the scope of spread or survival of organisms and their products or otherwise reduce the risk of introducing an organism into the environment, can be used to achieve safety. An experiment involving planned introduction into the environment is considered safe only when conducted under conditions determined with reasonable certainty to have acceptable or negligible risk to human health or to managed or natural ecosystems.

For guidance, general principles and practices of confinement for safely conducting research are discussed. However, the appropriate design for a specific experiment will depend on the biological and ecological properties of the organism and the environmental factors unique to the research site. Examples that illustrate the application of the confinement principles are provided in Appendix 1.

~~Recommendations for confinement of specific groups of organisms are included in Appendix 2.~~

~~Confinement seeks to limit the potential of organisms to adversely affect human health or managed or natural ecosystems.~~

IX-A. Application of Confinement Principles.

The ~~level of~~ confinement measures used should correspond~~s~~, in general, to the level of safety concern. Therefore, the need to apply confinement measures to achieve safety ~~level of confinement~~ is related to the potential for maintaining or increasing pest/pathogen status, the nature of the ecological relationships in the environment, the potential for establishment in the environment, the potential for inducing genetic change in natural or managed populations, the potential for monitoring and control, the characteristics of the accessible environment, and the ~~design~~ objectives of the research. Some organisms~~, by virtue of their ability to cause adverse effects of predictably high consequence in the environment,~~ cannot be safely managed ~~handled~~ outside contained facilities and these organisms are designated LSC-3. ~~Level of Safety Concern 5.~~ Other organisms are designated LSC-1, ~~Level of Safety Concern 1,~~ because they pose acceptable or negligible risk to ~~involve little or no risk of adversely affecting~~ human health or managed or natural ecosystems~~, or because their characteristics of concern are of a self-limiting~~

~~nature and, therefore, require no or minimal confinement beyond that normally practiced on a well managed research farm or facility.~~ without the need for confinement measures beyond those inherent in the biology of the organism and the environmental characteristics of the particular site. The planned introduction into the environment of other organisms can only be safely managed by the use of additional appropriate confinement measures.

In addition to confinement principles utilized apply to mitigate risk, all research should conform with scientific principles and practices that are generally accepted in the specific discipline. Generally accepted practices have in common some of the following features:

1. An acceptable experimental design that states the objectives, methods and procedures; describes the site; defines the source, type, and identity of the organisms used; and defines the treatments.

2. Training and supervision of personnel in safety and emergency procedures, good laboratory practices, and animal care.

3. Maintenance of verifiable records including, in addition to experimental data, an appropriate inventory of experimental units, including losses; a record of changes in the protocol and the reasons for the change; and records pertaining to maintenance of site integrity.

4. Appropriate use of statistical methods in designing the study and evaluating the data.

5. Safe disposal of excess materials at termination of the study.

Before any materials (e.g., crops or animals raised during the study) are considered for use as food for humans or animals, the principal investigator must determine whether such materials comply with regulations of the U.S. Food and Drug Administration issued under the Federal Food, Drug and Cosmetic Act, and regulations of USDA's Food Safety and Inspection Service issued under the Federal Meat Inspection Act and the Poultry Products Inspection Act.

IX-B. Confinement Measures

Confinement measures can be placed ~~grouped~~ into five groups ~~types~~--physical, biological, environmental, chemical, and scale. The examples given for each group ~~type~~ are not inclusive of all options available. The principal investigator is encouraged to consult data bases in USDA's National Biological Impact Assessment Program (NBIAP). The NBIAP data bases, which can be accessed free of charge from a personal computer, provide detailed information to assist investigators in selecting an appropriate safety protocol for specific organisms. For more information about NBIAP telephone (202) 401-4892; telefax (202) 401-4888, or write to "The National Biological Impact Assessment Program, Room

330 G Aerospace Building, 901 D. Street, S.W., Washington, D.C. 20250-2200."

IX-B-1. Biological. The inherent biological properties of an organism greatly affect its behavior in a specific environment. These properties include, for example with plants, whether the growth habit is annual or perennial, and whether the flowering characteristics, natural means of pollination and pollen dissemination permit cross-pollination with other plants.

Biological approaches can be used to limit survival and dissemination of organisms outside the research site and to limit the transfer of genetic information from the research organism to other organisms. Such biological approaches include genetic modifications that disable the organism, that produce sterility, and that reduce the ability of the organism to survive or to escape predators. Removal of reproductive organs and removal of organisms that are hosts for the research organism can be used to aid confinement. Permitting natural biological decay, e.g., normal death, is a further effective approach.

IX-B-2. Environmental. The choice of the research site relative to the geographical location and surrounding ecosystem, taking into account the biological and ecological attributes of the research organism, is important to creating a safe experimental design. Environmental variables, which might be utilized to be reproduction-

limiting or to limit survival time and dissemination, include climate, geography or location of the research site (e.g., isolation from potential pollination species), water and nutrient supply, humidity, photoperiod, and availability of predators or host organisms in the area. Seasonal or temporal factors, i.e., time of year, may be extremely useful as well. Environmental factors can inherently contribute to the safety of a particular experimental design.

IX-B-1. Physical. Physical barriers can be used to limit the survival and dissemination of organisms outside the research site. Physical barriers include border rows, ~~geographical isolation,~~ dams, soil terraces, tillage, fences, screens, meshes, and impervious or plastic barriers.

~~IX-B-2. Biological. Biological barriers can be used to limit survival and dissemination of organisms outside the research site and to limit the transfer of genetic information from the research organism to other organisms. Biological barriers include genetic modifications that disable the organism, that produce sterility, and that reduce the ability of the organism to survive or to escape predators. Removal of reproductive organs and removal of organisms that are hosts for the research organism can be used to aid confinement. Natural biological decay, e.g., normal death, is a further barrier.~~

~~IX-B-3. Environmental. Environmental conditions can be varied to limit reproduction of organisms and to limit survival or dissemination of organisms outside the research site. Environmental variables, which are reproduction-limiting, include climate, geography or location of research site, water supply, humidity, and photoperiod. Seasonal or temporal factors, i.e., time of year, may be extremely important.~~

IX-B-4. Chemical. Chemical treatments can be used to limit survival and reproduction of organisms outside the research site and to limit transfer of genetic information from the research organism to other organisms. Chemical treatments include application of herbicides, fungicides, insecticides, disinfectants, fumigants, and other materials toxic to the research organism, pH ~~Ph~~ alterations, use of gametocides and other chemicals which act as reproductive control agents, and elimination of essential nutrients.

IX-B-5. Scale. By decreasing the number of organisms or the size of the research site, the possibility of rapid and widespread dissemination may be reduced. Remedial actions are easier to implement for smaller numbers of organisms and smaller research sites.

IX-C. Confinement Levels

~~Four levels of confinement are described below, ranging from good agricultural research practices (Confinement Level 1) to very stringent measures (Confinement Level 4). There~~

~~is a continuous progression from minimum confinement to maximum confinement, and each confinement level is based upon good agricultural research practices. Confinement measures are combined to achieve progressively greater stringency of confinement.~~

Confinement should be designed for each particular organism and specified accessible environment, based on the ability of the organism to escape ~~confinement~~ from the research site and cause unacceptable effects on managed or natural ecosystems. ~~The increased number and variety of confinement practices (e.g., the use of more than one type of biological barrier, or the use of a combination of biological and physical barriers) will result in greater assurance of safety~~ safe confinement. ~~These confinement levels are briefly described below. Consult Appendix 2 for details on confinement measures appropriate for each confinement level.~~

Confinement is divided into two levels.

IX-C-1. Confinement level 1. Organisms designated LSC-1, pose acceptable or negligible risk to human health or managed or natural ecosystems, their characteristics of concern typically are of a self-limiting nature at the chosen research site, and they require no additional confinement measures beyond those inherent in the biology of the organism and the environmental characteristics of the research site. Principal investigators should adhere to

practices generally accepted by the scientific discipline for the type of research study, including the general practices defined in Section IX-A.

~~IX-C-1. Confinement Level 1. Confinement Level 1 consists of good agricultural research practices for the organism in the accessible environment. Good agricultural research practices include, but are not limited to: acceptable experimental design; definition of source, type, and name of all research organisms; maintenance of beginning and ending inventory; careful record keeping, including significant alterations of research protocols; description of site design and layout; utilization of appropriate statistical analysis design; clear statements of objectives, procedures, and methods; control and maintenance of integrity of sites and organisms; training, instruction, and oversight of personnel on research and emergency procedures; appropriate termination of research and disposal of organisms and experimental material in excess of that retained for further research.~~

XI-C-2. Confinement level 2. Organisms designated LSC-2 require additional confinement measures to achieve planned introduction into the environment with acceptable risk. The confinement measure(s) should be designed to be effective in managing the identified risk. There is no set number or type of confinement that should be used, as the performance of the confinement measure(s) selected in

mitigating risk is the important determinant. For example, if dissemination of pollen is the only identified risk factor and dissemination can be prevented by preventing flower formation, a single measure that adequately prevents flower formation will be sufficient. In some cases it may be necessary to utilize a combination of confinement measures (e.g., the use of more than one type of biological barrier, or the use of a combination of biological and physical barriers) to achieve reasonable certainty that the planned introduction into the environment poses acceptable or negligible risk.

~~IX-C-2. Confinement Level 2. Confinement Level 2 consists of good agricultural research practices plus increased stringency of two or more of the confinement measures most appropriate to the organism. Confinement Level 2 is appropriate for Level of Safety Concern 2 modified organisms.~~

~~IX-C-3. Confinement Level 3. Confinement Level 3 consists of the use of good agricultural research practices plus increased stringency of three or more of the confinement measures most appropriate to the organism. Confinement Level 3 is appropriate for Level of Safety Concern 3 modified organisms.~~

~~IX-C-4. Confinement Level 4. Confinement Level 4 consists of the use of good agricultural research practices plus all available containment measures appropriate to the~~

~~organism. Confinement Level 4 is appropriate for Level of Safety Concern 4 modified organisms.~~

IX-D. Monitoring

Monitoring the movement or persistence of genetically modified organisms, their progeny or products, can provide useful information for designing future experiments and verifying the effectiveness of confinement measures. In some cases elaborate monitoring designs may be important in achieving a safe experiment, while in other cases minimal monitoring (e.g., visual observations during the course of the study) may be sufficient. The decision to monitor and the development of an appropriate monitoring protocol should be a flexible process that draws upon all pertinent available information. Investigators are urged to supply monitoring data to USDA's National Biological Impact Assessment Program so that it can be made available to other investigators through an NBIAP data base on monitoring currently under development.

X. Roles and Responsibilities

X-A. Institution

Each institution conducting or sponsoring ~~agricultural~~ research involving the planned introduction into the environment of genetically modified organisms ~~within the scope of the Guidelines should promote safe practices in conducting~~ is responsible for safety of the research and compliance with applicable regulations. Fulfilling this

responsibility requires at least the following activities:~~—~~ ~~Institutions are encouraged to:~~

X-A-1. Establishment and implementation of policies that include confirmation that organisms used and conditions of research are assessed in accordance with the principles of the Guidelines; ~~Establish and implement policies which provide for the safe conduct of research taking into account the points to consider presented in these voluntary Guidelines;~~

X-A-2. Ensuring that principal investigators responsible for research involving planned introduction into the environment of genetically modified organisms comply with the Guidelines and all applicable regulations and assisting them in doing so; and

X-A-3. Ensuring that concerns of the community about planned introductions into the environment of genetically modified organisms are solicited and addressed by the institution. ~~Establish or associate with an Institutional Biosafety Committee to aid principal investigators in using the Guidelines;~~

X-B. Institutional Biosafety Committee and other Experts

Principal investigators may wish to seek advice from institutional biosafety committees and others expert in assessing the safety of a proposed experiment and designing adequate safety procedures.

X-C. Principal Investigator.

On behalf of the institution, principal investigators are generally responsible for conducting research in a safe manner. As part of this responsibility, principal investigators are encouraged to:

X-C-1. Determine whether local, state, or federal regulations and guidelines apply and adhere to the requirements;

X-C-2. Consider the principles for safety assessment and design of safety protocols described in the Guidelines; and

X-C-3. Instruct and train their staffs in practices and techniques to achieve ~~maximise~~ safety and in procedures for dealing with accidents.

XI. Amendment Procedure

Proposals to change the Guidelines may be made by anyone through a written request for amendment to OAB. OAB will notify the submitter in writing that the request has been received and indicate the procedure for reviewing the request. Normally, OAB will publish the request in the Federal Register announcement for the next ABRAC meeting, if received in time for publication and if space is available on the ABRAC agenda. The Assistant Secretary for Science and Education will make a final determination on the request, usually after receiving a recommendation from ABRAC.

* U.S. G.P.O.:1992-311-403:60030/CSRS